This Week in The Journal

Purine Receptors Drive Shape Changes in Human Microglia

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(see pages 1373–1388)

Microglia continually extend processes into surrounding brain tissue, searching for signs of injury. Small disturbances cause microglia to extend additional processes toward the injury to remove toxic substances, whereas larger disturbances induce more pronounced morphological and molecular changes, including retraction of processes, proliferation, and secretion of inflammatory mediators and growth factors. These responses are often beneficial, but they can also exacerbate damage. Interventions that promote beneficial actions and/or inhibit detrimental effects might therefore improve clinical outcomes. Unfortunately, identifying candidate targets is difficult, because microglial phenotypes vary greatly across brain areas, injury types, and time after injury. Moreover, healthy human microglia exhibit gene expression patterns that differ somewhat from those of mice (Masuda et al., 2019, *Nature* 566:388). Therefore, studies of human microglia under various conditions are essential for identifying potential therapeutic targets.

Milior et al. examined microglia in living brain tissue obtained from people with tumors or epilepsy. Microglia were morphologically heterogeneous: some were ramified, continually extending and retracting long processes, while others—particularly those in more severely damaged tissue—were amoeboid and largely immobile. Regardless of initial morphology, however, microglia responded to laser-induced tissue injury by extending processes toward the injury site. In mice, such process extension is induced by release of purines from damaged cells. Likewise, application of low doses of purines induced process extension in both ramified and amoeboid microglia in human tissue. In contrast, high doses of purines induced process retraction.

In mouse microglia, purines induce process extension by acting on P2Y12 receptors and induce retraction by acting on A2A receptors. Milior et al. found that all human microglia expressed P2Y12 receptors and that P2Y12 antagonists prevented process extension in re-

sponse to purines or tissue damage. A2A receptors were less widespread in human microglia, however, and an antagonist of these receptors did not prevent purine-induced process retraction. Instead, process retraction was blocked by a combination of P2Y1 and P2Y13 receptor antagonists.

These data suggest that mouse and human microglia exhibit similar morphological responses to extracellular purines and tissue damage, but these responses are mediated partly by different receptors. More importantly, the study opens the door to future investigations of microglia in living human tissue, which should provide more insight into how these cells limit or exacerbate damage in different conditions.

Microglia from human peritumoral cortex (top left) and human epileptic hippocampal CA1 (top right), dentate gyrus (bottom left), and subiculum (bottom right). See Milior et al. for details.

Light Is Needed for Memory Maintenance in *Drosophila*

Show Inami, Shoma Sato, Shu Kondo, Hiromu Tanimoto, Toshihiro Kitamoto, et al.

(see pages 1427–1439)

Light has profound influences on our lives: it not only allows us to see, but also regulates circadian rhythms, which in turn regulate me-

tabolism and physical activity. Light also influences mood, as is clearly evident in people with seasonal affective disorder. Light even influences human cognition, likely in part by increasing arousal and attention. Light also affects cognition in other animals: keeping diurnal rats in low-light conditions impairs spatial memory (Yan et al., 2019, *Horm Behav* 111:78), and Inami et al. report that light is required for long-term memory maintenance in *Drosophila*.

Inami et al. subjected flies to courtship conditioning, in which a male fly is caged with a nonreceptive, previously mated female for 7 h. Because the male's attempts at courtship are continually rebuffed, he stops trying, and will refrain from courting even virgin females for up to 5 d. But males kept in total darkness for 2 d after conditioning spent more time in courtship behaviors on day 5 than those housed in normal light–dark conditions, suggesting that long-term memory was impaired. Notably, neither mild sleep deprivation nor keeping flies in constant light impaired memory, indicating that the effect of darkness was not a consequence of disrupted circadian rhythms or insufficient sleep. Furthermore, long-term memory was restored in dark-housed flies by activating brain photoreceptor neurons that release the peptide pigment-dispersing factor (Pdf). In contrast, silencing Pdf neurons or knocking down Pdf expression selectively during the memory-maintenance period disrupted long-term memory in normal light conditions. Finally, knocking out Pdf receptors or housing conditioned flies in constant darkness reduced expression of the cAMP-response-element-binding protein CrebB in mushroom-body α/β neurons, where CrebB was required for long-term memory maintenance.

These results suggest that light exposure in the days after conditioning promotes long-term maintenance of courtship-related memory in male *Drosophila*. The effects of light are likely mediated by activation of Pdf-expressing photoreceptors in the brain and by downstream activation of CrebB in mushroom-body neurons. Whether light is required for maintenance of other forms of memory in flies or mammals remains to be tested.

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